IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : Elliott Richelson et al.
Serial No.: 09/016,685
Filed : January 30, 1998
Title : USING POLYAMIDE NUCLEIC ACID OLIGOMERS TO ENGENDER A BIOLOGICAL RESPONSE

Art Unit: 1635
Examiner: S. McGarry

Assistant Commissioner for Patents
Washington, DC 20231

DECLARATION UNDER 37 CFR §1.132 OF ELLIOTT RICHELSON

I, Elliott Richelson, declare as follows:

1. I am a citizen of the United States and presently live at 109 Teal Pointe Lane, Ponte Vedra Beach, FL 32082-1936.

2. I am presently employed by Mayo Foundation, and have been so employed since 1975.

3. I received a Doctor of Medicine Degree from Johns Hopkins University, School of Medicine, Baltimore, MD.

4. I am an inventor on the above-indicated patent application.

5. I have read the Examiner's Office Action mailed July 12, 2000.

6. Neither I, my co-inventors, nor individuals under our supervision performed *in vivo* screening to identify neurotensin-1 receptor-specific PNA oligomers having *in vivo* activity prior to administering the NTR1-PNA oligomer to a mammal. The NTR1-PNA oligomer was the first PNA oligomer targeting the non-coding strand of rat neurotensin-1 receptor that I, my co-inventors, or individuals under our supervision, administered to a mammal. As described in the above-indicated patent application, a sequence specific biological response was detected after *in vivo* administration of the NTR1-PNA oligomer. In addition, neither I, my co-inventors, nor individuals under our supervision have established a cell culture screening method capable of identifying neurotensin-1 receptor-specific PNA oligomers having biological activity.

7. Neither I, my co-inventors, nor individuals under our supervision performed *in vivo* or cell culture

screening to identify mu-1 morphine receptor-specific PNA oligomers having *in vivo* activity prior to administering the MU1R-PNA oligomer to a mammal. The MU1R-PNA oligomer was the first PNA oligomer targeting the non-coding strand of rat mu-1 morphine receptor that I, my co-inventors, or individuals under our supervision, administered to a mammal. As described in the above-indicated patent application, a sequence specific biological response was detected after *in vivo* administration of the MU1R-PNA oligomer.

8. In a related patent application having serial number 08/953,269, I understand that the Examiner indicated that the experiment identical to the experiment presented in Example 3 of above-indicated patent application should be repeated using a PNA control. Individuals under my supervision conducted experiments using the SERT PNA described in Example 3 of the above-indicated patent application and a control PNA oligomer. The control PNA oligomer had a scrambled sequence with respect to that of the SERT PNA. No statistically significant difference between SERT PNA-treated animals and control PNA-treated animals was detected when behavioral activity was measured. In addition, no statistically significant difference between the levels of serotonin transporter protein measured in the SERT PNA-treated animals and control PNA-treated animals was detected.

9. Neither I, my co-inventors, nor individuals under our supervision performed *in vivo* or cell culture screening to identify rat dopamine transporter-specific PNA oligomers having *in vivo* activity prior to administering the antisense DAT-PNA oligomer described in the DAT manuscript (a scientific manuscript submitted for publication entitled "Altering behavioral responses and dopamine transporter protein with antisense peptide nucleic acids") to a mammal. The antisense DAT-PNA oligomer was the first PNA oligomer targeting the non-coding strand of rat dopamine transporter that I, my co-inventors, or individuals under our supervision, administered to a mammal. As described in the DAT manuscript, a sequence specific biological response was detected after *in vivo* administration of the antisense DAT-PNA oligomer.

10. Neither I, my co-inventors, nor individuals under our supervision performed *in vivo* or cell culture screening to identify rat angiotensinogen-specific PNA oligomers having *in vivo* activity prior to administering the sense-angiotensinogen PNA oligomer described in the angiotensinogen manuscript (a scientific manuscript submitted for publication entitled "Peptide nucleic acids specifically cause antigene effects *in vivo* by systemic injection") to a mammal. The sense-angiotensinogen PNA oligomer was the first PNA oligomer targeting the coding strand of rat angiotensinogen that I, my co-inventors, or individuals under our supervision, administered to a mammal. As described in the angiotensinogen manuscript, a sequence specific biological response was detected after *in vivo* administration of the sense-angiotensinogen PNA oligomer.

11. Individuals under my supervision conducted two experiments using a PNA oligomer targeting the coding strand of rat dopamine D2 receptor (sense DOP-PNA). In each experiment, animals treated with the

sense DOP-PNA exhibited significantly more catalepsy than animals treated with saline. The level of dopamine D2 receptor protein was measured in each experiment. In one experiment, animals treated with the sense DOP-PNA exhibited a significant reduction in the level of dopamine D2 receptor protein measured. In the other experiment, no statistically significant difference was detected in the levels of dopamine D2 receptor protein measured. In a separate experiment, a PNA oligomer targeting the non-coding strand of rat dopamine D2 receptor (antisense DOP-PNA) was administered to animals. In that experiment, animals treated with antisense DOP-PNA exhibited significantly more catalepsy than animals treated with saline. The levels of dopamine D2 receptor protein were not measured in this experiment. The sense DOP-PNA oligomer was the first PNA oligomer targeting the coding strand of rat dopamine D2 receptor that I, my co-inventors, or individuals under our supervision, administered to a mammal. The antisense DOP-PNA oligomer was the first PNA oligomer targeting the non-coding strand of rat dopamine D2 receptor that I, my co-inventors, or individuals under our supervision, administered to a mammal. Neither I, my co-inventors, nor individuals under our supervision performed *in vivo* or cell culture screening to identify dopamine D2 receptor-specific PNA oligomers having *in vivo* activity prior to administering the sense DOP-PNA and antisense DOP-PNA oligomers to a mammal.

12. Individuals under my supervision conducted experiments using a PNA oligomer targeting the coding strand of rat β-amyloid precursor protein (sense β-APP-PNA) and a control PNA oligomer similar to the sense β-APP-PNA with the exception that it contained a mismatch at every third nucleotide position (mismatch β-APP-PNA). The levels of Aβ(1-40) and Aβ(1-42) protein were measured in three experiments. In one of the three experiments, no statistically significant difference was detected between the levels of Aβ(1-42) protein measured in sense β-APP-PNA-treated animals and mismatch β-APP-PNA-treated animals. In the other two experiments, however, animals treated with the sense β-APP-PNA exhibited a significantly lower level of Aβ(1-42) protein when compared to the level exhibited in animals treated with the mismatch β-APP-PNA. In all three experiments, no difference was detected between the levels of Aβ(1-40) protein measured for the two treatment groups. It is noted that a PNA oligomer targeting the non-coding strand of rat β-amyloid precursor protein (antisense β-APP-PNA) was administered to animals. After administration, the levels of Aβ(1-40) and Aβ(1-42) protein were measured and compared to the levels measured in animals treated with saline. No statistically significant difference was detected, and no further experiments were conducted using the antisense β-APP-PNA. It also is noted that a second PNA oligomer targeting the coding strand of rat β-amyloid precursor protein (sense β-APP-PNA2) and a second PNA oligomer targeting the non-coding strand of rat β-amyloid precursor protein (antisense β-APP-PNA2) were administered to animals. After administration, the levels of Aβ(1-40) and Aβ(1-42) protein were measured and

compared to the levels measured in animals treated with saline. No statistically significant difference was detected, and no further experiments were conducted using sense β-APP-PNA2 or antisense β-APP-PNA2. The sense β-APP-PNA and sense β-APP-PNA2 oligomers were the first two PNA oligomers targeting the coding strand of rat β-amyloid precursor protein that I, my co-inventors, or individuals under our supervision, administered to a mammal. The antisense β-APP-PNA and antisense β-APP-PNA2 oligomers were the first two PNA oligomers targeting the non-coding strand of rat β-amyloid precursor protein that I, my co-inventors, or individuals under our supervision, administered to a mammal. Neither I, my co-inventors, nor individuals under our supervision performed *in vivo* or cell culture screening to identify rat β-amyloid precursor protein-specific PNA oligomers having *in vivo* activity prior to administering the antisense β-APP-PNA, antisense β-APP-PNA2, sense β-APP-PNA, and sense β-APP-PNA2 oligomers to a mammal.

13. Individuals under my supervision conducted one experiment using a PNA oligomer targeting the coding strand of the protein component of human telomerase (sense TEL-PNA), a control PNA oligomer similar to sense TEL-PNA with the exception that it contained a mismatch at every third nucleotide position (mismatch TEL-PNA), and the PNA oligomer designated MU1R-PNA in the above-identified patent application. In this experiment, animals treated with the sense TEL-PNA exhibited significantly less tumor growth than animals treated with either the mismatch TEL-PNA or the MU1R-PNA. In a separate experiment, tumors from animals treated with the sense TEL-PNA exhibited a significantly lower level of telomerase activity when compared to the level measured in tumors from animals treated with saline. Telomerase activity experiments were not performed using the mismatch TEL-PNA or MU1R-PNA controls. The sense TEL-PNA oligomer was the first PNA oligomer targeting the coding strand of the protein component of human telomerase that I, my co-inventors, or individuals under our supervision, administered to a mammal. Neither I, my co-inventors, nor individuals under our supervision performed *in vivo* or cell culture screening to identify human telomerase, protein component-specific PNA oligomers having *in vivo* activity prior to administering the sense TEL-PNA oligomer to a mammal.

14. I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize

the validity of the instant patent application or any patent issuing thereon.

Dated: 1/11/01

Elliott Richelson

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